

**REMARKS**

Claims 1-3, 5-18, 20-22, 32, 34 and 35 were pending in this application. Claims 2, 9 and 20 are now cancelled without prejudice to Applicants' right to prosecute their subject matter in the present application and in related applications. Claims 1, 3, 10, 14, 15, 16, 17, 22, 32, 34 and 35 are currently amended without any intent of disclaiming equivalents thereof. Applicants submit the amendments to the claims introduce no new matter. Accordingly, upon entry of this paper, claims 1, 3, 5-8, 10-18, 22, 32, 34 and 35 are pending and presented for consideration.

**Amendments to the Specification**

Applicants amend the specification herein, pursuant to 37 CFR 1.71(g)(1), to add a paragraph identifying a Joint Research Agreement between Instrumentation Laboratory S.p.A. and T.A.C. Thrombosis and Coagulation Aktiebolag. Applicants also enclose herewith the necessary fee for the amendment as set forth in 37 CFR 1.17(i).

**Claim Objections**

Claims 1, 3, 10, 17, 22 and 34-35 are objected to because of various informalities. Applicants amend claims 1, 3, 10, 17, 22 and 34-35 herein to clarify the claimed invention. Applicants respectfully submit that the amendments to the claims overcome the objections and request reconsideration and withdrawal of the objections.

**Rejections under 35 U.S.C. § 112, First Paragraph**

Claims 3, 8-9, 17-18, 20, 22, 32, and 34-35 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

First, the Office action alleges that claims 3, 8, 9 and 18, each claim reciting an element in which the open-ended transition term "comprise" is used, are not supported in the specification because the use of "comprise" in the claim includes not only the recited component, but may also include an unlimited number of additional components. The Office action alleges that the Applicants must provide support for each of these unlimited additional components in order to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

Applicants submit that the rejection is inappropriate and request reconsideration and withdrawal of the rejection.

“[T]he law makes clear that the specification need teach only one mode of making and using a claimed composition. … [T]here is no requirement that the specification enable every mode for making and using the claimed products.” Amgen, Inc. v. Hoechst Marion Roussel, Inc., 126 F.Supp.2d 69, 160 (D. Mass. 2001) (citations omitted). Applicants further submit that the specification, figures and claims, as originally filed, provide sufficient description to enable one of skill in the art to make at least one mode of the claimed composition. For example, support for a particle comprising at least latex can be found at paragraphs [0054] and [0067]-[0069], and support for a first member comprising at least Protein S can be found at paragraphs [0033] and [0052]. Applicants respectfully request reconsideration and withdrawal of the rejections.

Second, the Office action alleges that claims 9 and 18 are not supported in the specification because the specification does not specifically recite that the fragment of C4BP is “a fragment of C4BP that binds protein S.” Applicants again submit that the specification, figures and claims as originally filed, in light of the state of the art at the time of filing, enabled one of skill in the art to practice the invention claimed in claims 9 and 18 because the protein S binding site on C4BP was well known in the art at the time the present application was filed. The specification need not disclose what is well known to those skilled in the art in order to satisfy the enablement requirement. See In re Buchner, 929 F.2d 660, 661 (Fed. Cir. 1991).

Applicants submitted in the April 15, 2007 response as evidence of the state of the prior art as of the filing date, a scientific paper by Hardig Y., *et al.* published in 1996, prior to the priority date of the present application, reporting that the entire protein S-binding site on C4BP is located within β-chain N-terminal short consensus repeat 1 (SCR-1). See Hardig Y., *et al.* (1996) “The amino-terminal Module of the C4b-binding Protein β-chain Contains the Protein S-binding Site,” J. Biol. Chem., 271:20861-20867, a copy of which was provided with Applicants’ April 15, 2007 response and the arguments of which are incorporated by reference herein. Therefore, Applicants submit that one skilled in the art would readily understand what structure

is required for a fragment of C4BP that binds to protein S. Therefore, Applicants submit that claims 9 and 18 are sufficiently enabled.

Moreover, the Office action does not address the Hardig evidence or Applicants' remarks presented in the April 15, 2007 response in the rejection of claims 9 and 18 under 35 U.S.C. § 112, first paragraph. See Office action at pages 5-6. Accordingly, Applicants respectfully request reconsideration in light of the evidence previously presented and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Third, the Office action alleges that one of two possible interpretations of claim 17 is not supported in the specification. Applicants amend claim 17 to clarify that the sample contains a molar ratio of the third member to the first member of between about 10 and 40. Support for this amendment can be found in the specification as originally filed at least at paragraph [0042]. Applicants submit that the clarifying amendment to claim 17 obviates the rejection and request reconsideration and withdrawal of the rejection.

Finally, the Office action alleges that the limitation "the second member and the third member do not bind each other" in claim 18 is not supported in the specification. Applicants submit that direct support for this limitation can be found in the specification as originally filed at paragraph [0043]. Specifically, paragraph [0043] teaches that "the second member 2BP and the third member 3BP do not significantly bind to each other." Emphasis added. Applicants submit that the claim is sufficiently described in the specification and request reconsideration and withdrawal of the rejection.

#### **Rejection under 35 U.S.C. § 112, Second Paragraph**

Claims 1-17, 22, 32 and 34-35 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Without acquiescing to the rejection, and solely to advance prosecution, Applicants amend claims 1, 16, 17 and 32 to further clarify the claimed subject matter. Applicants submit that the amendments overcome the rejections and respectfully request reconsideration and withdrawal of the rejections.

**Rejection under 35 U.S.C. § 102: David**

Claims 1-3, 5-7 and 10-12 were rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 4, 486,530 to David et al. (“David”). Applicants traverse the rejection to the extent it is maintained over the claims as amended.

Claim 1, as amended, recites a method for detecting an unbound form of a first member of a binding pair in a sample containing both the unbound form and a bound form of the first member by, *inter alia*, forming a second complex comprising a first particle, a second member, the first member, a third member, and a second particle, wherein the second member comprises “C4b-binding protein (C4BP) or a fragment of C4BP that binds to protein S” and the third member comprises “an antibody which specifically binds to the first member.”

Applicants submit that David does not teach or suggest such a method. Instead, David teaches a method for detecting an antigen using a two-site immunometric assay that relies upon the formation of an antibody:antigen:antibody sandwich. According to David’s method, two different monoclonal antibodies generated against two different binding sites on the antigen are added to a sample. David teaches that both antibodies are necessary to complete the immunometric sandwich. See David at column 6, line 54 – column 7, line 2.

David does not teach or suggest the use of a binding member other than a monoclonal antibody. More specifically, David does not teach or suggest a method wherein at least one of the binding partners is a natural binding partner of the antigen, for example, C4BP or a fragment of C4BP that binds protein S.

Moreover, David does not teach or suggest that David’s method may be used to detect an unbound form of a binding pair in a sample containing both the unbound form and a bound form of the first member. Instead, David teaches a generic method for detecting the presence of an antigenic substance using monoclonal antibodies obtained by the selection of a monoclonal antibody from a population of mouse hybridomas generated against the antigen. However, David’s monoclonal antibody generation discussion does not teach or suggest a method for generating antibodies capable of detecting only the unbound form of the first member of a

binding pair in a sample containing both the unbound form and a bound form of the first member.

Furthermore, although David teaches various particle agglutination assay embodiments using monoclonal antibodies at column 9, line 58 through column 10, line 50, Applicants submit that David does not disclose the relationship of the particles and the associated monoclonal antibodies in sufficient detail to anticipate Applicants' claimed method.

In one embodiment, David discloses antibodies bound to particles in which "each particle carr[ies] a plurality of antibodies." David at column 9, lines 61-64. In another embodiment, David teaches creating a mixture of a quantity of particles to which a first monoclonal antibody is bound with a quantity of particles to which a second monoclonal antibody is bound. However, David then teaches that this arrangement results in "a milky suspension," instead of and in contrast to a detectable particle clump associated with agglomeration or agglutination resulting in a change in turbidity as required by Applicants' claimed method. See David at column 9, lines 64-68.

Another of David's embodiments teaches the formation of agglomeration or agglutination of the particles to form an easily detectable particle clump. See David at column 9, line 68 through column 10, line 32. However, David teaches that particle agglutination occurs when antibodies specific to a polyvalent antigen are introduced to a suspension. In this embodiment, David does not clarify the relationship of the various antibodies to the particles (such that David may teach agglutination only in the situation where each particle contains multiple varieties of monoclonal antibodies). Furthermore, this embodiment requires the introduction of antibodies (plural) specific to a polyvalent antigen. This teaching implies that detection of a polyvalent antigen is not possible by a change in turbidity unless at least two distinct monoclonal antibodies are used as binding partners.

Applicants submit that David fails to anticipate claim 1 and its dependent claims because David does not teach or suggest the use of a binding member other than a monoclonal antibody. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

**Rejection under 35 U.S.C. § 103: David in view of Giri**

Claims 8-10, 18, 20, 22, 32 and 34 were rejected under 35 U.S.C. § 103(a) as being unpatentable over David in view of Giri et al., Thomb.Haemost. 1998 Apr; 79(4):767-72 (“Giri”). Applicants traverse the rejection to the extent it is maintained over the claims as amended.

David was discussed above with respect to amended independent claim 1, from which claims 8-10, 18, 20, 22, 32 and 34 depend. Giri does not cure the deficiencies of David. As discussed above, David only teaches the use of two monoclonal antibodies to form an antibody:antigen:antibody immunometric sandwich to detect the presence of an antigen. David neither teaches nor appreciates the use of a binding partner other than an antibody to detect an antigen in a two-site immunometric assay. Moreover, David does not teach or suggest that David’s method may be used to detect an unbound form of a binding pair in a sample containing both the unbound form and a bound form of the first member.

Giri does not teach a method for detecting protein S using particles and detecting the formation of a second complex by measuring an increase in the turbidity of the sample. Instead, Giri teaches a direct enzyme-linked ligandsorbent assay (ELSA) using a binding member immobilized on a microtiter plate and requiring the further addition of a detectable substrate, for example, peroxidase, to identify isolated protein S. See Giri at pages 767-768, “Subjects, Materials and Methods.” Additionally, the ELSA solid substrate assay taught by Giri is time consuming, difficult, and expensive to automate.

As discussed in Applicants’ specification as originally filed at paragraphs [0009] and [0010], Giri does not teach or suggest that Giri’s method may be used to detect an unbound form of a binding pair in a sample in the presence of both the unbound form and the bound form of the first member. Instead, Giri requires the separation of bound protein S (the bound form of the first member) from free protein S (the unbound form of the first member) either during the preanalytical step, by precipitation of bound protein S with polyethyleneglycol, or during the

development of the immunoassay, by washing away the complex that does not bind to the solid phase. See Giri at page 768, left column.

Applicants submit that it would not have been obvious to combine the teachings of David and Giri to arrive at the claimed method. On the contrary, although David may suggest the use of monoclonal antibodies to detect a polyvalent antigen, David neither provides an invitation to try binding partners other than monoclonal antibodies nor suggest how binding partners other than monoclonal antibodies might be used in David's method. Applicants submit that the Office action improperly focuses on the alleged obviousness of substitutions and differences, instead of looking at the combination of elements to result in *the invention as a whole*. See Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1382-83 (Fed. Cir. 1986).

Because the detection of unbound protein S provides one of the most valuable parameters for the clinical diagnosis of thrombotic disease, it is desirable to provide a rapid, low-cost, analyte detection method able to detect and quantitate the amount of unbound protein S in a sample which does not require separating bound from unbound forms of protein S. Accordingly, Applicants submit that Applicants' claimed method provides a solution to an unmet need in the market for automated thrombotic disease diagnostic assays and provides a commercial advantage over the method taught by Giri.

Applicants submit that neither David nor Giri, either alone or in combination, teach or suggest the claimed method. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

**Rejection under 35 U.S.C. § 103: David in view of Ballas**

Claim 13 was rejected under 35 U.S.C. § 103(a) as being unpatentable over David in view of U.S. Patent No. 4,812,395 to Ballas et al. ("Ballas"). Applicants traverse the rejection to the extent it is maintained over the claims as amended.

David was discussed above with respect to amended independent claim 1, from which claim 13 depends. Ballas does not cure the deficiencies of David. Ballas does not teach or

suggest an immunometric antigen detection method wherein at least one of the binding partners is a natural binding partner of the antigen, for example, C4BP or a fragment of C4BP that binds protein S.

Applicants submit that neither David nor Ballas, either alone or in combination, teach or suggest the claimed method. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

**Rejection under 35 U.S.C. § 103: David in view of Mischak**

Claims 14-17 were rejected under 35 U.S.C. § 103(a) as being unpatentable over David in view of U.S. Patent No. 6,124,430 to Mischak et al. (“Mischak”). Applicants traverse the rejection to the extent it is maintained over the claims as amended.

David was discussed above with respect to amended independent claim 1, from which claims 14-17 depend. Mischak does not cure the deficiencies of David. Mischak does not teach or suggest an immunometric antigen detection method wherein at least one of the binding partners is a natural binding partner of the antigen, for example, C4BP or a fragment of C4BP that binds protein S.

Furthermore, with respect to claims 14 and 15, which specify the molar ratios of the two binding partners used in the claimed method, the second member (comprising C4BP or a fragment of C4BP that binds to protein S) and the third member (an antibody which specifically binds to the first member), Applicants submit that Mischak does not teach or suggest modifying the molar ratios of two *binding partners* used in the assay, as required by Applicants’ amended claims 14 and 15.

Applicants submit that neither David nor Mischak, either alone or in combination, teach or suggest the claimed method. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

**Rejection under 35 U.S.C. § 103: David in view of Giri and Cambiaso**

Claim 35 was rejected under 35 U.S.C. §103(a) as being unpatentable over David in view of Giri in further view of U.S. Patent No. 4,184,849 to Cambiaso et al. (“Cambiaso”).

Applicants traverse the rejection to the extent it is maintained over the claims as amended.

David and Giri were discussed above with respect to amended independent claim 1, from which claim 35 depends. Cambiaso does not cure the deficiencies of David and Giri. Cambiaso does not teach or suggest an immunometric antigen detection method wherein at least one of the binding partners is a natural binding partner of the antigen, for example, C4BP or a fragment of C4BP that binds protein S. Instead, Cambiaso teaches a mixed agglutination assay to detect the presence of antibodies or antigens in a liquid by mixing the liquid with first and second particulate reagents which mutually agglutinate but whose agglutination is inhibited by the particular antibody or antigen in the liquid under assay. See Cambiaso at Abstract and columns 1 and 2.

Applicants submit that none of David, Giri or Cambiaso, either alone or in combination, teach or suggest the claimed method. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

**Nonstatutory Obviousness-Type Double Patenting**

Claims 1-3 and 5-17 were rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,379,975 to Linse et al. (“Linse”) in view of David.

Claims 1-3, 5-18, 20, 22 and 34-35 were rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-41 of U.S. Patent No. 7,041,458 to Dahlback (“Dahlback”) in view of David.

Claim 32 was rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of Linse in view of David as applied to claim 8 above, or alternatively over claims 1-41 of Dahlback as applied to claim 8 above, and further in view of Giri.

David and Giri were discussed above with respect to amended independent claim 1. Applicants submit that neither Linse nor Dahlback is available as prior art under one or more of 35 U.S.C. §102(e), (f) or (g) via 35 U.S.C. §103(c)(2) because of the existence of a joint research agreement. The assignee of record of each of Linse and Dahlback, T.A.C. Thrombosis and Coagulation Aktiebolag, is a party to a joint research agreement with Instrumentation Laboratory S.p.A, an organization owned and controlled by the Werfen Group, who also owns and controls the current assignee of record of the claimed invention, Biokit, S.A. The joint research agreement was made effective on July 1, 1997, before the filing date of the claimed invention. Further, the claimed invention was made as a result of activities undertaken within the scope of the joint research agreement and by or on behalf of the parties to the joint research agreement, T.A.C. Thrombosis and Coagulation Aktiebolag and Instrumentation Laboratory S.p.A. Finally, the specification of the instant application is herein amended to disclose the names of the parties to the joint research agreement; T.A.C. Thrombosis and Coagulation Aktiebolag and Instrumentation Laboratory S.p.A.

Applicants submit that the existence of the joint research agreement obviates the double patenting rejections and respectfully request reconsideration and withdrawal of the rejections.

### CONCLUSION

Applicants believe that claims 1, 3, 5-8, 10-18, 22, 32, 34 and 35 are in condition for allowance. The Examiner is invited to telephone the undersigned attorney to discuss any remaining issues. Early and favorable actions are respectfully solicited.

Respectfully submitted,



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